A new scoring system in cancer genetics: application to criteria for BRCA1 and BRCA2 mutation screening.

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carrier conditional to his/her family history, and to compare the performance of this new scoring system with the Manchester scoring system and to the exact probability. We also used the score system on a sample of 4563 families from the Institut Curie in Paris tested for BRCA1/2 mutations and present the results here.

METHODS

Disease model

We consider a predisposing cancer syndrome, due to a dominant mutated gene, involved in various tumour localisations j and various tumour characteristics c, such as the ‘triple-negative’ (TN) phenotype in breast cancer or the MSI phenotype in colorectal cancer. Let F(t; g; j) be the cumulative risk of developing a tumour at localisation j by age t (in years) for carrier status g (g=1 for a carrier and g=0 for a non-carrier). For affected individuals, the probability of tumour characteristic c is designed by ρ(c; g; j). An observation is defined by (s, c, t), where s equals 1 or 0 according to the affected status of the individual, and t is age at onset for affected persons and censored age for unaffected ones. The probability \( \Phi(s, c; t; g; j) \) of this observation depends on carrier status g and on localisation j:

\[
\Phi(s, c; t; g; j) = (F(t + 1; g; j) - F(t; g; j))\rho(c; g; j) \quad \text{if } s = 1
\]

\[
= 1 - F(t + 1; g; j) \quad \text{if } s = 0
\]

Sex is directly taken into account by considering different values of j for men and women for a same localisation.

Elaboration of the scoring system

The scoring system is proposed as a surrogate for the probability of a proband, in a given family, to be a mutation carrier. This scoring system is derived from a conditional probability \( P \), which equals 1 or 0 according to the affected status of the individual, and \( t \) is age at onset for affected persons and censored age for unaffected ones. The probability \( \Phi(s, c; t; g; j) \) of this observation depends on carrier status g and on localisation j:

\[
\Phi(s, c; t; g; j) = (F(t + 1; g; j) - F(t; g; j))\rho(c; g; j) \quad \text{if } s = 1
\]

\[
= 1 - F(t + 1; g; j) \quad \text{if } s = 0
\]

The scoring system is proposed as a surrogate for the probability of a proband of family member i with the proband (0 for the proband, 1 for the carrier) of being affected by at least one localisation and 0 if not, \( I_{ij} = 1 \) if the individual is affected by at least one localisation and 0 if not, \( I_{ij} = 1 \) if the individual is affected by localisation j and 0 if unaffected, and

\[
\Lambda(s_i, c_i, t_i; j) = \frac{\Phi(s_i, c_i, t_i; j)}{\Phi(s_i, c_i, t_i; 0, j)}
\]

If \( s = 1 \), this ratio is the relative risk for a carrier of being affected by a tumour of localisation j.

Using this approximation (S), one neglects the fact that a person affected with a given cancer is unaffected by the other cancer localisations and considers that cancers for a given individual occur independently.

The computation of the global score S for a family is then obtained by summing the elementary scores:

\[
\begin{aligned}
&\Phi(s, c; t; g; j) = (F(t + 1; g; j) - F(t; g; j))\rho(c; g; j) \\
&= 1 - F(t + 1; g; j)
\end{aligned}
\]

\[
\text{if } s = 0
\]

Sex is directly taken into account by considering different values of j for men and women for a same localisation.

Application to the diagnosis of BRCA1/2-associated breast-ovarian cancer predisposition

Carriers of BRCA1/2 gene mutations have an increased risk not only of breast and ovarian cancer but also of pancreas and prostate cancer. In addition, it has been shown that the type of breast pathology, particularly TN tumours, that is, negative for oestrogen receptor (ER), progesterone receptor (PR) and HER2 expression, influences the probability of detecting a BRCA1 mutation, but not a BRCA2 mutation.

For assessing the ratios of probabilities \( \Lambda(s, c, t; j) \) necessary to the determination of the scores, penetrance values were taken from the meta-analysis of Chen and Parmigiani for female breast cancer and ovarian cancer, from Tai et al. for male breast cancer and from van Asperen et al. and Rischof for...
pancreas and prostate cancers. In cases where the risks at greater ages were not provided by these sources, we inferred the missing data from available data by fitting a mixture model with a subgroup of non-susceptible carrier individuals and a subgroup of susceptible carriers for which the risk is modelled by a Weibull function. This model is very similar to the ‘cured model’ of de Angelis,21 also used for penetrance estimation in the genotype-restricted likelihood method.22 Cumulative risks in the general population used were those published for France based on data of cancer registries.23

Probabilities for the TN status of a breast tumour were obtained from the proportion of TN tumours among women tested for BRCA1/2 data in studies without any selection on morphological characteristics.15 24 25 Weighting these proportions by the number of women, we obtained an average proportion of TN of 68% among women with BRCA1 mutation and 13% among women with no BRCA1 mutation (including those with a BRCA2 mutation).14

Mutations in BRCA1 and BRCA2 are rare and involved in breast cancer in almost equal proportions26 for the two genes. Neglecting the very infrequent occurrence where individuals are carriers for both genes, one on BRCA1 and one on BRCA2, we computed \( \lambda(s_i, c_i, t_{ij}) \) as the average of risks associated with the mutations of the two genes weighted by the frequency of mutation carriers on each gene. For allele frequencies, estimates as different as 0.00126 and 0.00515 for both genes were found. We used an intermediate value of 0.001 for each gene, which was shown to best fit published data27–31 for frequency of carriers among affected individuals.14

**Evaluation of the performance of the new scoring system**

The performance of the new scoring system was evaluated using simulations of families with breast and/or ovarian cancer. The main advantage of simulations compared with observed data is to provide an estimation of absolute sensitivity, that is, the proportion of carrier individuals that fulfil the criteria recommended for genetic testing among all affected ones, whereas observed data only provide an estimation of relative sensitivity of criteria among the only families that underwent genetic testing.

The simulation of pedigrees was performed in order to be representative of families of individuals affected by breast-ovarian cancer in the French general population. We considered an affected case, the proband, his/her age (not exceeding 80 years); sex and phenotype (breast, including male breast cancer, or ovarian cancer) were drawn at random according to the birth cohort of the mother. The value of \( \lambda \) was chosen to fit female fertility in France. Note that we use \( x_i+1 \) instead of \( x_i \) to account for the minimum interval between two births at 1 year.

Fertility could be interrupted either by death or by reaching the end of reproductive period (age exceeding 49).

The birth ranks of the proband and of his/her parents within their own sibships were set at random from a uniform distribution.

The resulting pedigrees include at least three generations, from the proband’s grandparents to the proband and his/her first cousins, and, if the proband and his/her cousins are old enough to have children, the pedigrees include a fourth or even a fifth generation.

The genotype of each member of the family conditional on the proband’s genotype was simulated following Mendel laws and using Bayes’ theorem. Their phenotype (disease status and tumour characteristics) was simulated using the parameters mentioned above.

We simulated a total of 10 000 000 families, and we computed for each family its conditional probability \( P \) that the proband is a mutation carrier given the personal and family history of the disease (H), without knowledge of the simulated genotype, the Manchester combined score (MCS)13 and the score obtained by the new system (NSS). The probability \( P \) was computed using the Elston–Stewart algorithm14 and is referred as \( P \)robability computed using the Elston–Stewart algorithm (PREST). For each of the three methods (PREST, MCS, NSS), the sensitivity was estimated as the proportion of families with a score (or a probability \( P \)) above a given threshold, among families with a mutation carrier proband. Similarly, the specificity at this threshold was estimated as the proportion of families with a score (or a probability \( P \)) below the threshold, among families with a non-carrier proband. The positive predictive value (PPV) was estimated as the proportion of carriers among the families exceeding this threshold. The performance of the three systems was compared by receiver operating characteristic (ROC) curves, which represent sensitivity as a function of one minus specificity for various threshold values, and also by the curve of PPV as a function of sensitivity.

**Family sample**

The scoring system was used on a sample 4563 families screened for BRCA1 and BRCA2 mutations between 1995 and 2012 in the Institut Curie in Paris. These families have been tested following the current recommended criteria in France.3 13 35 Probands had given their informed consent for BRCA1/2 genetic testing in the setting of a family cancer clinic and their consent to the use of their anonymised data. Probands and relatives who gave authorisations to their medical record access were informed of the computer recording of their family history. The family database had been declared to the French national ad hoc authority (CNIL). As the study does not involve intervention on patients, there was no need to consult an ethics committee. The point and small-size mutation analyses of the BRCA1 and BRCA2 genes have been performed from 1995 to the present by different screening methods, followed by Sanger sequencing of amplicons showing abnormal screening patterns: DGGE, DHPLC and EMMA. Regarding large gene rearrangements of both genes, they have been searched using DNA combing, and later QMPSF and EMMA.
RESULTS

Simulated families

The values of the new BRCA1/2 mutation scores for the different members of a family, according to cancer localisation and type (TN status for breast cancer), age class at diagnosis and degree of kinship with the proband are given in table 1 for affected members and in table 2 for unaffected members. The score values displayed were obtained by multiplying the original scores by 2 and by rounding them to integer values in order to be easily summed by hand. As expected, for cancer at a given age and localisation, the proband always has the highest score compared with his/her relatives, and the scores of relatives decrease with increasing degree of kinship with the proband.

Figure 1 shows the ROC curves for the new scoring system, for the PREST probability and for the Manchester scoring system. Figure 2 shows PPV as a function of sensitivity for these three systems. In figures 1 and 2, the PREST curves show that the PREST method performs the best. The NSS curves are consistently closer to the PREST curves than the MCS curves. The area under the ROC curve is 0.92 for PREST, 0.88 for the Manchester scoring system and 0.90 for the new system.

To investigate the performance gained in accounting for unaffected family members and for the degree of kinship of relatives with the proband, we compared the PPV curves of the NSS with that of a NSS modified to ignore either unaffected family members or kinship coefficients, and finally both. Each information type alone slightly improves the prediction and taken into account all together substantially increases the performance of the system, as shown by the PPV curves (figure 3).

Table 3 gives the average probability Pr0 obtained by PREST for various score values of the simulated families, the probability Pr1 estimated from the proportion of simulated families with a mutation among those with a score within each score class, and the probability Pr2 expected from the approximations made for elaborating the score (see the relationship between P and S in the ‘Methods’ section). The observed proportion Pr1 is very close to the Pr0 probability calculated by PREST for all values of scores. The probability Pr2 is very close to Pr0 and Pr1 for moderate values of scores but slightly deviates from these probabilities as the score increases.

Table 4 shows the sensitivity, PPV and specificity of the NSS for various values of the score threshold recommended for genetic testing. For comparison, we calculated these parameters for the Manchester scoring system with a threshold of 16 assumed to correspond to a threshold mutation probability of 10%. The sensitivity was 72%, the PPV was 16% and the specificity was 88%. We obtained similar PPV and specificity with the new system for a score threshold of 5, but the sensitivity was higher at 77% (see table 4). We recommend this score threshold of 5 to ensure a good sensitivity.

Table 1 New scores for the proband and affected relatives in the family (reprinted by permission from Bulletin du Cancer)

<table>
<thead>
<tr>
<th>Age class (years)</th>
<th>First-degree relative</th>
<th>Second-degree relative</th>
<th>Third-degree relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>11</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>20–29</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>30–39</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>40–49</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>50–59</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>60–69</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>≥70</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Women with ovarian cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>20–29</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>30–39</td>
<td>8</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>40–49</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>≥60</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Men with breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>23</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>30–39</td>
<td>16</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>40–49</td>
<td>11</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>50–59</td>
<td>10</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>60–69</td>
<td>8</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>≥70</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Triple-negative tumours (if information available)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>-2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pancreas cancer</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2 New scores for unaffected relatives (reprinted by permission from Bulletin du Cancer)

<table>
<thead>
<tr>
<th>Age class (years)</th>
<th>First degree</th>
<th>Second degree</th>
<th>Third degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30–49</td>
<td>-0.3</td>
<td>-0.1</td>
<td>0</td>
</tr>
<tr>
<td>50–69</td>
<td>-0.7</td>
<td>-0.4</td>
<td>-0.2</td>
</tr>
<tr>
<td>≥70</td>
<td>-1</td>
<td>-0.4</td>
<td>-0.2</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30–49</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50–69</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥70</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1 Receiver operating characteristic curves for the probability of mutation (PREST), the new scoring system (NSS) and the Manchester combined score system (MCS).
The online supplementary appendix gives an example of computation of score in a family. The maternal branch reaches the score of 9 and would lead to \( \text{BRCA1/2} \) screening as it largely exceeds the score threshold of 5 that we recommend. The Manchester score would be 16, which is exactly the threshold recommended for mutation screening.

Families screened at the Institut Curie

Both NSS and PREST were computed in the 4563 families. The scores range from \(-4\) to 31 (to the exception of a single family with a score of 48, which was discarded from the plots). Figure 4 shows the frequency polygons of the score values, separately in families where no mutation was found and in families where a \( \text{BRCA1/2} \) mutation was found. Figure 5 illustrates the good concordance of the score and PREST values by showing the score plotted against the transformation of PREST (P) given at the very end of the ‘Methods’ section.

Table 3  Probability of mutation according to score values in the new system

<table>
<thead>
<tr>
<th>Score class</th>
<th>Pr0</th>
<th>Pr1</th>
<th>Pr2</th>
</tr>
</thead>
<tbody>
<tr>
<td>[0, 1]</td>
<td>0.01</td>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>[1, 2]</td>
<td>0.01</td>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>[2, 3]</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>[3, 4]</td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>[4, 5]</td>
<td>0.03</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>[5, 6]</td>
<td>0.03</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>[6, 7]</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>[7, 8]</td>
<td>0.08</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>[8, 9]</td>
<td>0.12</td>
<td>0.13</td>
<td>0.12</td>
</tr>
<tr>
<td>[9, 10]</td>
<td>0.18</td>
<td>0.18</td>
<td>0.18</td>
</tr>
<tr>
<td>[10, 11]</td>
<td>0.25</td>
<td>0.26</td>
<td>0.27</td>
</tr>
<tr>
<td>[11, 12]</td>
<td>0.35</td>
<td>0.37</td>
<td>0.38</td>
</tr>
<tr>
<td>[12, 13]</td>
<td>0.47</td>
<td>0.49</td>
<td>0.50</td>
</tr>
<tr>
<td>[13, 14]</td>
<td>0.57</td>
<td>0.58</td>
<td>0.62</td>
</tr>
<tr>
<td>[14, 15]</td>
<td>0.66</td>
<td>0.67</td>
<td>0.73</td>
</tr>
<tr>
<td>[15–16]</td>
<td>0.74</td>
<td>0.75</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Pr0, probability of mutation obtained by PREST; Pr1, probability estimated from the proportion of simulated families with a mutation; Pr2, probability expected from the approximation made for elaborating the score.

Table 4  Performance of the new scoring system according to threshold for recommending genetic testing

<table>
<thead>
<tr>
<th>Score threshold</th>
<th>Sensitivity</th>
<th>Positive predictive value</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.93</td>
<td>0.06</td>
<td>0.57</td>
</tr>
<tr>
<td>2</td>
<td>0.89</td>
<td>0.08</td>
<td>0.69</td>
</tr>
<tr>
<td>3</td>
<td>0.86</td>
<td>0.10</td>
<td>0.76</td>
</tr>
<tr>
<td>4</td>
<td>0.82</td>
<td>0.12</td>
<td>0.82</td>
</tr>
<tr>
<td>5</td>
<td>0.77</td>
<td>0.15</td>
<td>0.87</td>
</tr>
<tr>
<td>6</td>
<td>0.71</td>
<td>0.21</td>
<td>0.92</td>
</tr>
<tr>
<td>7</td>
<td>0.65</td>
<td>0.29</td>
<td>0.95</td>
</tr>
<tr>
<td>8</td>
<td>0.59</td>
<td>0.38</td>
<td>0.97</td>
</tr>
<tr>
<td>9</td>
<td>0.54</td>
<td>0.48</td>
<td>0.98</td>
</tr>
<tr>
<td>10</td>
<td>0.49</td>
<td>0.57</td>
<td>0.99</td>
</tr>
<tr>
<td>11</td>
<td>0.44</td>
<td>0.66</td>
<td>0.99</td>
</tr>
<tr>
<td>12</td>
<td>0.39</td>
<td>0.74</td>
<td>0.99</td>
</tr>
<tr>
<td>13</td>
<td>0.34</td>
<td>0.79</td>
<td>0.99</td>
</tr>
<tr>
<td>14</td>
<td>0.30</td>
<td>0.84</td>
<td>0.99</td>
</tr>
<tr>
<td>15</td>
<td>0.26</td>
<td>0.87</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Figure 2  Positive predictive value as a function of sensitivity for the probability of mutation (PREST), the new scoring system (NSS) and the Manchester combined score system (MCS).

Figure 3  Positive predictive value as a function of sensitivity for the probability of mutation (PREST), the new scoring system (NSS) and the Manchester combined score system (MCS).
DISCUSSION

Our new scoring system is based on the conditional probability P that a proband is a carrier, given all relevant predictive information in the family. It is therefore possible to apply it to other cancer family syndromes such as Lynch syndrome or Li–Fraumeni syndrome, and even any disease with monogenic subentities due to specific gene mutations, such as Alzheimer or Parkinson disease. The only requirement is to know the relative risks of disease(s) in mutation carriers associated with predictive factors and the frequency of mutation carriers in the general population.

In breast–ovarian cancer, the most commonly used system for identifying BRCA1/2 mutation carriers in France is based on family configurations.13–14 This system was shown to perform rather well, but its performance is difficult to evaluate when new relevant criteria are added. Our new scoring system was shown to be an efficient alternative.14 Moreover, as any scoring system, it may be easily modified if new predictive factors are found and relevant information is available. In addition, the score threshold of 5 that we recommended may be easily modified if mutation screening cost decreases as expected in the near future.

An advantage of our method is to rely on theoretical foundations and not on an empirical calculation of scores from a sample of families selected on familial aggregation of breast or ovarian cancer cases. Indeed, a method based on observed proportion of mutations in such families should correct for the criteria recommended for genetic testing. This would probably be not even sufficient since not all families fulfilling these criteria are expected to undergo genetic testing. Such a bias likely explains the discrepancy in the proportion of mutations in families with low-score values between the families screened at the Institut Curie and those from the simulated sample.

The improvement of our new scoring system compared with the Manchester scoring system is mainly the result of incorporating degrees of kinship of relatives with the proband and unaffected relatives. This valuable improvement comes at the cost of a moderately more complicated computation of scores of families. In the pedigree given in the online supplementary appendix, the computation of scores may be achieved in a few seconds using the Manchester scoring system and in about 2 min with the new one. To overcome this complication, we proposed to use a two-step procedure, with first a rough screening on simple criteria3 by physicians for recommending genetic counselling followed, if judged relevant, by a fine evaluation by genetic counsellors using the new scoring system for recommending genetic testing.14

The approximation of the probability P that was made for elaborating the score system was found to be valid for moderate values of scores, but slightly differed from the true value as the score increased. This is only a minor drawback as any system would recommend genetic testing to the families that have such high-score values.
Another limit is that the system relies on uncertain values for disease risks. However, these risks should be known with increasing precision in the future and it will be possible to modify the score values and threshold accordingly. Note that this limit also holds for methods based on probability computations. This uncertainty on risks estimates might also affect the simulations but not the comparison between PREST and the score systems, given that the same parameters were used.

Finally, the model on which the scoring system is elaborated does not account for familial factors other than BRCA1 and BRCA2 that could be another source of familial aggregation. This is done, for instance, in the BOADICEA model, which includes, in addition to BRCA1/2 genes, a polygenic component and was shown to perform better for carrier prediction than other algorithms. Such an addition would have considerably complicated the elaboration of the score system and was not expected to have any impact on sensitivity, but might have slightly affected PPV and specificity.

In the present study, we used an original method that generates families as close as possible to real families in the general population, particularly by taking into account mortality at childbearing ages. The interest of using simulations is to provide estimations of absolute sensitivity, whereas observed data only provide relative sensitivity. For instance, using simulations permitted to demonstrate that criteria based on positive family history for BRCA1/2 genetic testing have low sensitivity.

Estimation of absolute sensitivity is important as recommendations for genetic testing more and more focus on this parameter, and not only on PPV. In this study, we have shown that the usual threshold probability of mutation of 10%, corresponding to a score threshold of about 8 in the new system (table 3), would lead to a low sensitivity of less than 60% (table 4). In addition, we must keep in mind that the observed proportion of families in which a mutation was found may be a poor estimation of PPV as they are most likely selected towards high values of scores. Indeed, families for which a test is recommended may not all undergo genetic testing, particularly when only a few family members are affected. Therefore, families with a score greater than a given threshold, say 5, have an overrepresentation of families with higher scores and are not representative of all families exceeding a score threshold of 5. Therefore, the value of 15% for PPV found from the simulations is probably a better estimation of this parameter than the proportion of nearly 20% found in the sample.

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